REMARKS

New claims 35 and 36 are supported by the limitations now canceled from claims 1 and 12. New claims 37 and 38 are supported by the disclosures in paragraphs [0007] and [0011]. New claims 39 and 40 are supported by Figure 3 of the specification.

Claim Rejections - 35 USC § 112

Claims 1-3, 5, 7, and 9-14 were rejected under 35 U.S.C. 112, second paragraph. This rejection is respectfully traversed and should be withdrawn in light of this Amendment.

Claim Rejections - 35 USC § 103

Claims 1-3, 5, 7, and 9-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cleve et al. (Mol. Cell. Probes (1998) 12:243-147) in view of Dimitrov et al (U.S. 2003/0013091), and further in view of Hildebrandt et al., "Surface-Enhanced Resonance Raman Spectroscopy of Rhodamine 6G Absorbed on Colloidal Silver," J. Phys. Chem., 1984, Vo1.88, pp.5935-5944, OR Kudelski et al., "Characterization of the copper surface optimized for use as a substrate for surface-enhanced Raman scattering," Vibrational Spectroscopy, 1998, Vo1.16, pp.21-29.

The Examiner states:

> Cleve teaches a method comprising: (a) obtaining a barcode comprising two or more tags attached to an organic molecule backbone (see page 245, columns 1 and 2, where the branched DNA amplifier molecule has 15 branches with four copies of a sequence which bind to labeled probes, where binding of the labeled probes will result in two or more tags attached in a noncovalent manner to an organic molecule backbone), (b) binding the barcode to a target (see page 245, column 2, where the probes are hybridized to a target), (C) detecting the barcode bound to the target (see page 246, subheading "Flow Cytometry", where the

> barcodes are individually detected). Wherein the organic molecule backbone comprises one or more branched nucleic acids (see page 245, column 1 and 2, where branched nucleic acids with 15 branches are used which are organic molecules) and the barcode is detected by a technique of fluorescence spectroscopy (see figure 1, and page 246, column 1, where fluorescence spectroscopy is used to measure the beads).

Applicants respectfully submit that Cleve does not teach a method comprising obtaining a barcode comprising two or more ***different types*** of tags branched to an organic molecule backbone as recited in claims 1 and 12. In fact, Examiner Freedman, the previous Examiner examining this application, had clearly stated on page 5, line 1 of the Office Action of April 23, 2007, that "Cleve does not teach the use of different labels on the branched DNA."

Cleve does ***not*** provide a figure showing the structure of the branched DNA used in Cleve. However, Cleve explains that the branched DNA has a preamplifier, amplifier and labeled probes. See last paragraph of column 1 and paragraph bridging first and second columns of page 245 of Cleve. Cleve also explains that "a nucleic-acid target is first captured in a microwell [or microbeads, rather than microwell] via immobilized capture oligonucleotides and solution-phase capture extenders (CE) oligonucleotides which form a bridge between the microwell-bound [or microbead-bound] oligonucleotide and the target." See paragraph bridging first and second column of page 243 of Cleve. Furthermore, Cleve explains that the preamplifier is attached to the target via a label extender. See last paragraph of column 1 of page 245 of Cleve. Based on the above description of the structure of the branched DNA used in Cleve, Applicants were able to obtain the attached reference entitled "Branched DNA Technology in Molecular Diagnostics" by Gregory J. Tsongalis, which clearly shows structure of the branched DNA of Cleve in Figure 1 of the Tsongalis reference.

Referring to branched DNA of Figure 1 of the Tsongalis reference and the barcode of the claimed invention, it is evident that the branched DNA of Cleve as

represented in Figure 1 of Tsongalis does not have two or more different tags. Examiner Freedman had stated on page 5, starting at line 6 of the Office Action of April 23, 2007, and the present Examiner has continued to maintain this position in the paragraph bridging pages 6 and 7 of the pending Action, that persons of ordinary skill in the art would have been motivated to use two or more different types of tags in the branched DNA of Cleve in view of Dimitrov since Cleve suggests using different types of colors on page 244, column 1, of Cleve. Applicants respectfully submit Cleve suggests using "beads of different colours" on page 244, column 1, of Cleve, but nowhere does Cleve suggest using two or more different types of tags in the branched DNA of Cleve.

In fact, as shown in Figure 1D of the Tsongalis reference, the tags (i.e., the label probes) are of the same type and are attached to the amplifier molecules, which in turn are attached to the preamplifier molecule. Cleve's branched DNA produces a few but large signals by combination of a plurality of probes attached to a plurality of amplifier molecules, which are attached to the preamplifier molecule. However, Cleve's branched DNA suffers from inadequate specificity which would result in high levels of false positives or false negatives as explained in paragraph [0004] in the Background section of the pending application. On the other hand, the barcodes of the present invention are substantially simpler in structure than that of Cleve's branched DNA while still avoiding the above-mentioned disadvantages of Cleve's branched DNA.

The Examiner has acknowledged that "Cleve does not teach the use of a plurality of barcodes on the branched DNA … ." See last paragraph of page 5 of the Action. The Examiner attempts to fill these gaps by resorting to Dimitrov, stating:

> Dimitrov expressly teaches the use of a plurality of barcodes since Dimitrov teaches that "Several unique combinations of labels can be formed using branched nucleic acids (see page 7, paragraph 0057)." Dimitrov further notes that "nucleic acids labeled with any or all of these combinations can be bound to another nucleic acid through hybridization (see page 7, paragraph 0055)."

Each of Cleve's branched DNA produces a unique signal that is distinguishable from other branched DNA of Cleve by tailoring the preamplifier, the number of amplifier molecules and the number of label probes hybridized to the amplifier molecules. In short, with so many degrees of freedom available to design each unique branched DNA of Cleve, persons of ordinary skill in this art would simply have had no motivation to further use different types of labeled probes (tags) in the branched DNA of Cleve. Applicants respectfully submit that persons of ordinary skill in this art would have interpreted Dimitrov's teaching that "Several unique combinations of labels can be formed using branched nucleic acids (see page 7, paragraph 0057)" as applied to Cleve to mean that the branched DNAs of Cleve could have many different distinguishable signals by tailoring preamplifier, the number of amplifier molecules and the number of label probes hybridized to the amplifier molecules. Persons of ordinary skill in this art would not have interpreted Dimitrov's teaching as a suggestion to modify Cleve's branched DNA to include different types of labeled probes (tags) in the branched DNA of Cleve.

The Examiner has also acknowledged that "Cleve also does not discuss the use of a signal enhancing surface comprising a salt located in proximity to the barcodes." See page 7, lines 11-12, of the Action. The Examiner has attempted to fill this gap by resorting to Hildebrandt or Kudelski. However, persons of ordinary skill in this art would not have been motivated to modify the method of Cleve by the addition of a salt located in proximity of the barcodes for the following reasons. First, as explained above, Cleve's branched DNA labels already have a very large signal to noise ratio. Thus, further amplification using a salt located in proximity to the branched DNA labels of Cleve would be an overkill. Second, the addition of salt in the "hybridization buffer" of Cleve (see page 245, first column, of Cleve), would change the buffer conditions, which would change the specificity, which in turn would result in high levels of false positives or false negatives.

Claims 1-3, 5, 7, 9-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Singer et al (U.S. Patent 6,534,266) in view of Urdea et al (U.S. Patent 5,635,352), in view of Horn et al (U.S. 2001/0009760), and further in view of Hildebrandt et al., "Surface-Enhanced Resonance Raman Spectroscopy of Rhodamine 6G Absorbed on Colloidal Silver," J. Phys. Chem., 1984, Vo1.88, pp.5935-5944, OR Kudelski et al., "Characterization of the copper surface optimized for use as a substrate for surface-enhanced Raman scattering," Vibrational Spectroscopy, 1998, Vo1.16, pp.21-29. This rejection is respectfully traversed.

The Examiner states, "Singer teaches a method of claims 1 and 12 comprising: (a) obtaining a plurality of barcodes, at least one of the plurality of barcodes comprising two or more different tags attached to an organic molecule backbone (see column 8, lines 6-38, where oligonucleotides have five different fluorophores attached to the nucleic acid probe backbone to form 31 different barcodes) … ." See page 9, lines 3-7, of the Action.

Applicants respectfully submit that Singer in fact fails to disclose "at least one of the plurality of barcodes comprising ***two or more different tags branched to an organic molecule backbone***." The barcodes of Singer do not have two or more different tags branched to an organic molecule backbone as the tags of Singer are attached to a strip. Furthermore, as recognized by the Examiner, "Singer does not teach the use of ***branched*** DNA probes." See page 10, line 11, of the Action.

Claims 1 and 12 have been amended to recite that the barcodes comprise two or more different types of tags attached ***branched*** to an organic molecule backbone. Singer clearly fails to disclose this limitation. The Examiner attempts to fill this gap in Singer by Urdea. However, Urdea also fails to disclose "at least one of the plurality of barcodes comprising ***two or more different tags branched to an organic molecule backbone***." Somewhat similar to the branched DNA label of the Tsongalis

reference, the branched DNA label of Urdea fails to disclose two more different tags branched to an organic molecule backbone.

Claims 1-3, 5, 7, and 9-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Woudenberg (US 7,198,900, filed 8/29/03), in view of Hildebrandt et al., "Surface-Enhanced Resonance Raman Spectroscopy of Rhodamine 6G Absorbed on Colloidal Silver," J. Phys. Chem., 1984, Vo1.88, pp.5935-5944, OR Kudelski et al., "Characterization of the copper surface optimized for use as a substrate for surface-enhanced Raman scattering," Vibrational Spectroscopy, 1998, Vo1.16, pp.21-29. This rejection is respectfully traversed.

The present application was filed on September 24, 2003, while the effective filing date of Woudenberg is August 29, 2003. Applicants intend to antedate Woudenberg by filing a declaration under 37 CFR 1.132. Thus, the rejection over Woudenberg in view of Hildebrandt or Kudelski should be held in abeyance.

In view of the above amendment, applicant believes the pending application is in condition for allowance. Applicants request a 2-month extension of time and submit related fees in the attached Petition. The Director is authorized to charge any additional fees necessary and/or credit any overpayments to Deposit Account No. 03-3975, referencing Docket No. 043395-0377977.

Respectfully submitted,

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